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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 May 2001 (25.05.2001)

PCT

(10) International Publication Number
WO 01/35959 A1

(51) International Patent Classification[7]: A61K 31/426, A61P 43/00 // C07D 277/22

(21) International Application Number: PCT/SE00/02252

(22) International Filing Date:
15 November 2000 (15.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9904177-4 18 November 1999 (18.11.1999) SE

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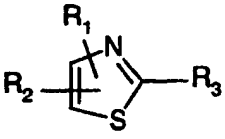
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

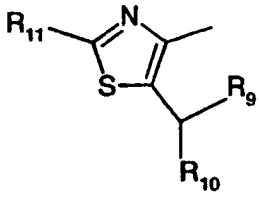
Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF THIAZOLE DERIVATIVES FOR TREATMENT/PREVENTION OF P38 KINASE MEDIATED DISORDERS



(I)



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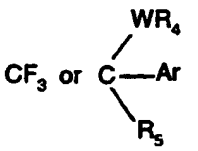
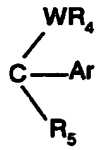


(a)



(b)

(57) Abstract: The present invention relates to the use of a compound of general formula (I) or (II) wherein R_1 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF_3; R_2 and R_3 are independently H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl, (a), with the proviso that one of R_2 or R_3 is (b) wherein W is O, S, NH or N-lower alkyl; R_4 is H, lower alkyl or lower acyl; R_5 is H, lower alkyl, aryl-lower alkyl, cyclopropyl or lower perfluoroalkyl; Ar is phenyl, furyl, thienyl, naphthyl, pyridyl or pyrrolyl, optionally substituted by R_6; R_6 is one or more groups selected from lower alkyl, lower acyl, halogen, lower alkoxy, CF_3, OH, NO_2 or NR_7R_8, wherein R_7 and R_8 independently are H, lower alkyl or lower acyl; R_9 is CH_2-halogen, CH_3 or COOH; R_{10} is H, OH or =O; R_{11} is H or OH; geometrical and optical isomers, tautomers and racemates thereof where such isomers or tautomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof, for the preparation of a medicament for the treatment and/or prevention of p38 MAP kinase mediated disorders.

WO 01/35959 A1

USE OF THIAZOLE DERIVATIVES FOR TREATMENT/PREVENTION OF P38 KINASE MEDIATED DISORDERS

Field of the invention

The present invention is related to the use of thiazole derivatives in the treatment and/or prevention of p38 kinase mediated disorders.

Background of the Invention

Mitogen-activated protein kinases (MAP kinases) are a family of proline-directed serine/threonine kinases, to date including extracellular regulated kinases (ERKs), c-jun N-terminal kinases (JNKs) and p38 MAP kinases. The catalytic mechanism of MAP kinases involves initial phosphorylation of a threonine residue and a tyrosine residue, binding of substrate and subsequently binding of adenosine triphosphate deep in the catalytic cleft. Next, transfer of phosphate to the bound protein substrate occurs. Activation of MAP kinases takes place when upstream regulatory protein kinases are stimulated by e.g. growth factors, inflammatory agents and neurotransmitters to phosphorylate MAP kinases.

The p38 MAP kinase family consists of at least five isoforms, named p38α, p38β, p38β2, p38γ and p38δ. Alternatively, the p38 MAP kinase proteins have been named stress-activated protein kinases (SAPK), together with the c-jun N-terminal kinase family. The p38 MAP kinases are specifically activated by bacterial lipopolysaccharide, osmotic stress, alkylating agents, pro-inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNFα) as well as by the neurotransmitter glutamate. Numerous substrates of p38 MAP kinases have been identified, including transcription factors (e.g. ATF-2, Elk-1, SAP-1, CHOP and MEF2C) as well as other kinases (MAPKAP kinases-2, -3, -5, MNKs-1, -2 and PRAK). Besides the direct substrates, the activity of other proteins such as the transcription factor NFκB can be indirectly affected. The regulation of numerous cellular genes has been shown to be dependent, at least in part, on p38 MAP kinase. Examples of affected genes and proteins are c-fos, c-jun, interleukin-1, cyclooxygenase-2 and phosphoenolpyruvate carboxykinase (PEPKC).

p38 MAP kinases have been implicated to be of importance in numerous human disorders and pathological conditions. These include disorders, which are clearly inflammatory in nature, such as rheumatoid arthritis, asthma and Crohn´s disease. In addition, it has recently become evident that p38 MAP kinases have pronounced roles in. for example, cerebral infarction or haemorrhage as well as cardiac infarction. Specifically, several independent lines of evidence have demonstrated that p38 MAP kinases have regulatory roles, for example on apoptotic responses, as well as during hypoxia and ischaemia, affecting cells of the central nervous system or cardiac myocytes.

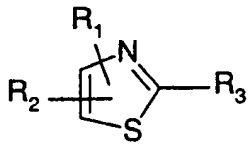
Previously, imidazole derivatives (e.g. 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole, SB 203580), pyrrole derivatives, and pyrrolopyridines (e.g. 6-amino-2-(4-fluorophenyl)-4-methoxy-3- (4-pyridyl)-1H-pyrrolo[2, 3-b]pyridine, RWJ 68354), pyrazole derivatives and bisarylureas have been shown to be potent inhibitors of p38 MAP kinase isoforms, with IC_{50} values in cellbased assays in the range of approximately 0,1-1 µM, see e.g. Henry JR et al. (1998): Potent inhibitors of the MAP kinase p38, Bioorganic and Medicinal Letters 8:3335-3340; De Laszlo SE (1998): Pyrroles and other heterocycles as inhibitors of p38 kinase, Bioorganic and Medicinal Letters 8:2689-2694; Henry JR et al. (1998): 6-Amino-2-(4-fluorophenyl)-4-methoxy-3-(4-pyridyl)-1*H*-pyrrolo(2,3-*b*)-pyridine (RWJ 68354): A potent and selective p38 kinase inhibitor. Journal of Medicinal Chemistry 41: 4196-4198; Gallagher TF et al (1995): 2,4,5-Triarylimidazole inhibitors of IL-1 biosynthesis, Bioorganic and Medicinal Chemistry Letters 5: 1171-1176; and Adams JL et al (1998): Pyrimidinylimidazole inhibitors of CSBP/p38 kinase demonstrating decreased function of hepatic cytochrome P450 enzymes, Bioorganic and Medicinal Chemistry Letters 8: 3111-3116, WO98/52937, WO98/52940, WO98/52941, WO98/52558, WO99/00357 and WO99/32463. The imidazole, pyrrole and pyrrolopyridine derivatives previously described are all believed to inhibit p38 MAP kinase activity by inhibiting binding of adenosine triphosphate to the kinase. In 1999, a new type of p38 MAP kinase inhibitor, LL-Z1640-2, was described by Takehana K, Sato S, Kobayasi T, Maeda T (1999): A Radicilol-related macrocyclic nonaketide compound, antibiotic LL-Z1640-2, inhibits the JNK/p38 pathways in signal-

specific manner, Biochem Biophys Res Comm 257:19-23. This compound acts as an inhibitor of events upstream of p38 MAP kinase activation as it has been described to inhibit the phosphorylation of p38 MAP kinase, in response to anisomycin, but not to tumor necrosis factor-α. When inhibition of expression of genes downstream of p38 MAP kinase by the above mentioned imidazole-derivative SB 203580 has been evaluated, expression of response genes such as *c-fos* or *c-jun* has been inhibited to 60 – 80%.

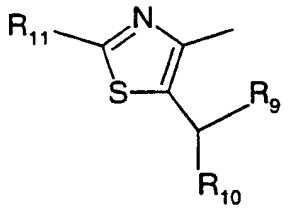
Brief Description of the Invention

The thiazole compounds of general formula I or II below according to the present invention are found to show usefulness in the treatment and/or prevention of p38 MAP kinase mediated disorders. The thiazole compounds are found to inhibit p38 MAP kinase pathways by a mechanism distinctly different from that of imidazole derivatives, such as SB 203580, and therefore provides new therapeutic potential. Another object of the invention is a pharmaceutical formulation comprising said thiazole compounds. Still another object of the invention is a combination treatment in the form of a thiazole compound according to the invention and another p38 MAP kinase inhibitor, which acts through a different mechanism, and therefore also affords a new therapeutic possibility.

These thiazole compounds have the general formula **I or II**



(I)

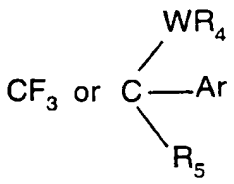


(II)

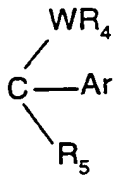
wherein

R_1 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF_3;

R_2 and R_3 are independently H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl,



with the proviso that one of R_2 or R_3 is



wherein W is O, S, NH or N-lower alkyl;

R_4 is H, lower alkyl or lower acyl;

R_5 is H, lower alkyl, aryl-lower alkyl, cyclopropyl or lower perfluoroalkyl;

Ar is phenyl, furyl, thienyl, naphthyl, pyridyl or pyrrolyl, optionally substituted by R_6;

R_6 is one or more groups selected from lower alkyl, lower acyl, halogen, lower alkoxy, CF_3, OH, NO_2 or NR_7R_8, wherein R_7 and R_8 independently are H, lower alkyl or lower acyl;

R_9 is CH_2-halogen, CH_3 or COOH;

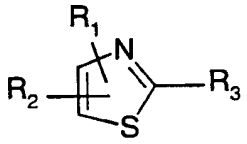
R_{10} is H, OH or =O;

R_{11} is H or OH;

geometrical and optical isomers, tautomers and racemates thereof where such isomers or tautomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof, for the preparation of a medicament for the treatment and/or prevention of p38 MAP kinase mediated disorders.

Detailed Description of the Invention

The present invention provides thiazole compounds having the general formula **I or II** for the treatment and/or prevention of p38 MAP kinase mediated disorders



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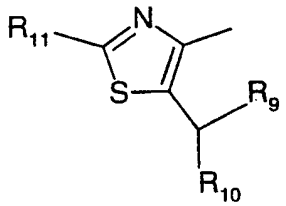
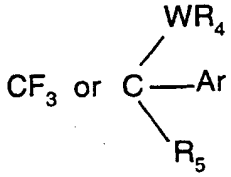


(II)

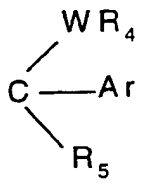
geometrical and optical isomers, tautomers and racemates thereof where such isomers or tautomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof,

wherein R_1 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF_3;

R_2 and R_3 are independently H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl,



with the proviso that one of R_2 or R_3 is



wherein W is O, S, NH or N-lower alkyl;

R_4 is H, lower alkyl or lower acyl;

R_5 is H, lower alkyl, aryl-lower alkyl, cyclopropyl or lower perfluoroalkyl;

Ar is phenyl, furyl, thienyl, naphthyl, pyridyl or pyrrolyl, optionally substituted by R_6;

R_6 is one or more groups selected from lower alkyl, lower acyl, halogen, lower alkoxy, CF_3, OH, NO_2 or NR_7R_8, wherein R_7 and R_8 independently are H, lower alkyl or lower acyl;

R_9 is CH_2-halogen, CH_3 or COOH;

R_{10} is H, OH or =O;

R_{11} is H or OH.

The following definitions shall apply throughout the specification and the appended claims.

In the present context lower alkyl may be a straight or branched C_1-C_6 alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl, t-butyl, n-pentyl, isopentyl, t-pentyl, neopentyl, n-hexyl or isohexyl.

In the present context lower alkoxy may be a straight or branched C_1-C_6 alkoxy, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, s-butoxy, t-butoxy,

n-pentyloxy, isopentyloxy, t-pentyloxy, neopentyloxy, n-hexyloxy or isohexyloxy.

In the present context halogen may be fluoro, chloro, bromo or iodo.

In the present context aryl may be phenyl or naphthyl.

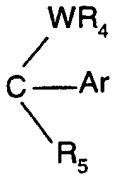
In the present context lower acyl may be lower alkyl-CO, aryl-CO or aryl-lower alkyl-CO.

The expression "pharmaceutically acceptable acid addition salts" is intended to include but is not limited to such salts as the hydrochloride, hydrobromide, hydroiodide, nitrate, hydrogen sulphate, dihydrogen phosphate, ethanedisulphonate, mesylate, fumarate, maleate, succinate, tartrate, citrate, lactate and malate.

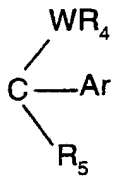
Throughout the specification and the appended claims, a given chemical formula or name shall encompass all geometrical and optical isomers, tautomers and racemates thereof where such isomers or tautomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof such as for instance hydrates.

R_1 is preferably H or lower alkyl.

R_2 and R_3 are preferably independently H, lower alkyl or



with the proviso that one of R_2 or R_3 is



W is preferably O or NH.

R_4 is preferably H.

R_5 is preferably H, lower alkyl or lower perfluoroalkyl.

Ar is preferably phenyl or furyl optionally substituted with halogen.

R_9 is preferably CH_2- halogen.

R_{10} and R_{11} are preferably H.

The most preferred compounds of formula **I** and **II** according to the present invention are 1-(4-methyl-5-thiazolyl)-1-phenylmethylamine and 5-(2-chloroethyl)-4-methylthiazole (clomethiazole), respectively. The compounds of general formula **I** and **II** may be prepared according to any methods described in GB 847 520, WO92/03134, WO95/01967, WO95/01968, WO95/01979, J. Am. Chem. Soc. 1935, 57, 1876-1881, Xenobiotica 1975, 5, 687-696, Dokl. Akad. Nauk SSSR 1971, 347-350 and J. Org. Chem. 1988, 53, 1748-1761.

Pharmaceutical Formulations

The administration of the thiazole compounds according to this invention alone or in combination with another p38 MAP kinase inhibitor, that acts through a different mechanism, may conveniently be oral, rectal, nasal, parenteral or by inhalation at a dosage level of, for example, about 1 to 3000 mg/kg, preferably about 10 to 1000 mg/kg and especially about 25 to 300 mg/kg and may be administered on a regime of 1 to 4 times a day. The dose will depend on the route of administration, a preferred route being by oral administration and a particularly preferred route being by intravenous infusion of an aqueous solution containing the compound of general formula I or II, in which case a

steady state plasma concentration of between 0.1 and 500 μM will be achieved. It will be appreciated that the severity of the disorder, the age of the patient and other factors normally considered by the attending physician will influence the individual regime and dosage most appropriate for a particular patient.

The other p38 MAP kinase inhibitor, which acts through a different mechanism, may be for example an imidazole derivative, a pyrrole derivative, a pyrrolopyridine derivative, a pyrazole derivative, a bisarylurea or a macrocyclic nonaketide compound.

The present compounds may also be used in co-therapies for the treatment of neurological disorders, such as together with tissue plasminogen activators, glutamate receptor antagonists, calcium-channel antagonists, other cation channel blockers, NOS inhibitors, radical scavengers, other kinase inhibitors, chemokine antagonists, purinergic antagonists or protease inhibitors.

The present compounds may also be used in co-therapies for the treatment of inflammatory disorders, such as together with steroids, cyclooxygenase-2 inhibitors, NSAIDs, immunosuppressive agents, 5-lipoxygenase inhibitors, LTB_4 antagonists and LTA_4 hydrolase inhibitors.

The pharmaceutical formulations comprising the compound of this invention may conveniently be tablets, pills, capsules, powders or granules for oral administration; sterile parenteral solutions or suspensions for parenteral administration; or as suppositories for rectal administration.

Medical and Pharmaceutical Use

Compounds of formula I or II would be useful for, but not limited to, the treatment of any disorder or disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated p38 MAP kinase activation in such a mammal. Accordingly, the present invention provides a method of treating a p38 MAP kinase mediated disorder,

which comprises administration of an effective p38 MAP kinase-interfering amount of a compound of formula, I or II, or a pharmaceutically acceptable salt thereof.

Compounds of formula I or II would be useful for, but not limited to, the treatment of inflammation in a subject.

Compounds of the invention would be useful to treat neurological disorders, including but not limited to cerebral ischaemia, stroke including cerebral infarction, cerebral haemorrhage and embolization to the vessels of the brain, multiple sclerosis, viral or bacterial infection and other inflammatory states of the central nervous system.

Compounds of the invention would be useful to treat hepatic diseases, including but not limited to alcoholic liver disease, liver cirrhosis, viral infections of the liver including infections with hepatitis viruses HAV, HBV, HCV, HDV and HEV.

Compounds of the invention would also be useful to treat arthritis, pulmonary disorders or lung inflammation, asthma, viral and bacterial infections and bone resorption diseases such as osteoporosis.

Compounds of the invention would also be useful to treat cachexia, cachexia secondary to infection or malignancy, including but not limited to cachexia secondary to acquired immunodefiency syndrome (AIDS), AIDS related complex (ARC), pneumonia, herpesvirus and hepatitisvirus.

Compounds of the invention would also be useful to treat autoimmune diseases, including but not being limited to rheumatoid arthritis, systemic lupus erythematosus (SLE), discoid lupus erythematosus (DLE), Sjögren´s syndrome, psoriasis, sarcoidosis, and graft-versus-host reactions.

Compounds of the invention would be useful to treat endotoxic shock, toxic shock syndrome, reperfusion injury, cardiovascular diseases including atherosclerosis, nephritis,

myalgia related to infection, gastrointestinal conditions including inflammatory bowel disease, such as Crohn´s disease and ulcerative colitis.

Compounds of the invention would be useful to treat ophthalmic diseases, neoplasia, metastasis, diabetic nephropathy, cardiomyopathy and disorders of the female reproductive system such as endometriosis.

Besides being useful for human treatment, these compounds may also be useful for veterinary treatment including mammals.

As used herein, the term "p38 MAP kinase mediated disorders" refers to any and all disorders and disease states in which p38 MAP kinases play a role, either by control of p38 MAP kinase itself, or by p38 MAP kinase causing another factor to be released, such as, but not limited to, IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to p38 MAP kinase, would therefore be considered a disorder mediated by p38 MAP kinase.

PHARMACOLOGY

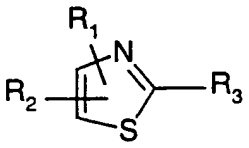
Biological evaluation

The present thiazole compounds have been evaluated biologically 1) in rat cortical glial cultures, 2) in human neuroblastoma cell lines and 3) in in vitro immunocomplex kinase assays

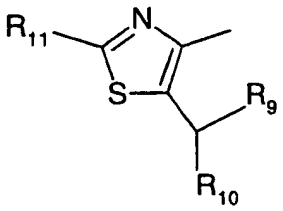
The results showed that the imidazole derivative 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole (SB 203580), but not 5-(2-chloroethyl)-4-methylthiazole (clomethiazole) or 1-(4-methyl-5-thiazolyl)-1-phenylmethylamine, inhibited p38 MAP kinase in this assay. The results demonstrate that the thiazole compounds of the invention and imidazole derivatives such as 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole act by different mechanisms when interfering with p38 MAP kinase pathways.

CLAIMS

1. The use of a compound of general formula I or II



(I)

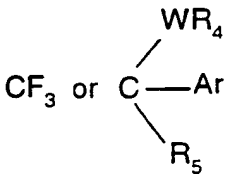


(II)

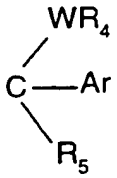
wherein:

R_1 is H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl or CF_3;

R_2 and R_3 are independently H, lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkyl,



with the proviso that one of R_2 or R_3 is



wherein W is O, S, NH or N-lower alkyl;

R_4 is H, lower alkyl or lower acyl;

R_5 is H, lower alkyl, aryl-lower alkyl, cyclopropyl or lower perfluoroalkyl;

Ar is phenyl, furyl, thienyl, naphthyl, pyridyl or pyrrolyl, optionally substituted by R_6;

R_6 is one or more groups selected from lower alkyl, lower acyl, halogen, lower alkoxy, CF_3, OH, NO_2 or NR_7R_8, wherein R_7 and R_8 independently are H, lower alkyl or lower acyl;

R_9 is CH_2-halogen, CH_3 or COOH;

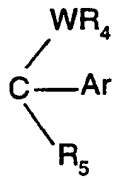
R_{10} is H, OH or =O;

R_{11} is H or OH;

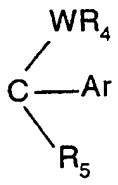
geometrical and optical isomers, tautomers and racemates thereof where such isomers or tautomers exist, as well as pharmaceutically acceptable acid addition salts thereof and solvates thereof, for the preparation of a medicament for the treatment and/or prevention of p38 MAP kinase mediated disorders.

2. The use of a compound of general formula **I** according to claim 1 characterized in that R_1 is H or lower alkyl.

3. The use of a compound of general formula **I** according to any one of claims 1 or 2 characterized in that R_2 and R_3 are independently H, lower alkyl or



with the proviso that one of R_2 or R_3 is



4. The use of a compound of general formula **I** according to any one of claims 1 to 3 characterized in that W is O or NH.

5. The use of a compound of general formula **I** according to any one of claims 1 to 4 characterized in that R_4 is H.

6. The use of a compound of general formula **I** according to any one of claims 1 to 5 characterized in that R_5 is H, lower alkyl or lower perfluoroalkyl.

7. The use of a compound of general formula **I** according to any one of claims 1 to 6 characterized in that Ar is phenyl or furyl optionally substituted with halogen.

8. The use of a compound of general formula **II** according to claim 1 characterized in that R_9 is CH_2- halogen.

9. The use of a compound of general formula **II** according to any one of claims 1 or 8 characterized in that R_{10} and R_{11} are H.

10. The use of a compound of general formula **I** according to any one of claims 1 to 7 characterized in that the compound is 1-(4-methyl-5-thiazolyl)-1-phenylmethylamine.

11. The use of a compound of general formula **II** according to any one of claims 1 or 8 to 9 characterized in that the compound is 5-(2-chloroethyl)-4-methylthiazole.

12. The use according to any one of claims 1 to 11 in the manufacture of a medicament for the treatment and/or prevention of inflammation, neurological disorders, multiple sclerosis, viral or bacterial infection and other inflammatory states of the central nervous system.

13. The use according to claim 12 in the manufacture of a medicament for the treatment and/or prevention of cerebral ischaemia, stroke including cerebral infarction, cerebral haemorrhage and embolization to the vessels of the brain.

14. The use according to any one of claims 1 to 11 in the manufacture of a medicament for the treatment and/or prevention of hepatic diseases.

15. The use according to claim 14 in the manufacture of a medicament for the treatment and/or prevention of alcoholic liver disease, liver cirrhosis, viral infections of the liver including infections with hepatitis viruses HAV, HBV, HCV, HDV and HEV.

16. The use according to any one of claims 1 to 11 in the manufacture of a medicament for the treatment and/or prevention of arthritis, pulmonary disorders or lung inflammation, asthma, viral and bacterial infections and bone resorption diseases such as osteoporosis.

17. The use according to any one of claims 1 to 11 in the manufacture of a medicament for the treatment and/or prevention of cachexia, cachexia secondary to infection or malignancy, including cachexia secondary to acquired immunodefiency syndrome (AIDS), AIDS related complex (ARC), pneumonia, herpesvirus and hepatitisvirus.

18. The use according to any one of claims 1 to 11 in the manufacture of a medicament for the treatment and/or prevention of autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus (SLE), discoid lupus erythematosus (DLE), Sjögren´s syndrome, psoriasis, sarcoidosis, and graft-versus-host reactions.

19. The use according to any one of claims 1 to 11 in the manufacture of a medicament for the treatment and/or prevention of endotoxic shock, toxic shock syndrome, reperfusion injury, cardiovascular diseases including atherosclerosis, nephritis, myalgia related to

infection, gastrointestinal conditions including inflammatory bowel disease, such as Crohn´s disease and ulcerative colitis.

20. The use according to any one of claims 1 to 11 in the manufacture of a medicament for the treatment and/or prevention of ophthalmic diseases, neoplasia, metastasis, diabetic nephropathy, cardiomyopathy and disorders of the female reproductive system such as endometriosis.

21. A method for the treatment and/or prevention of p38 MAP kinase mediated disorders by administering to a mammal including man in need of such a treatment a therapeutically effective amount of a compound defined in any one of claims 1 to 11.

22. A method according to claim 21 for the treatment and/or prevention of inflammation, neurological disorders, multiple sclerosis, viral or bacterial infection and other inflammatory states of the central nervous system.

23. A method according to claim 21 for the treatment and/or prevention of cerebral ischaemia, stroke including cerebral infarction, cerebral haemorrhage and embolization to the vessels of the brain.

24. A method according to claim 21 for the treatment and/or prevention of hepatic diseases.

25. A method according to claim 21 for the treatment and/or prevention of alcoholic liver disease, liver cirrhosis, viral infections of the liver including infections with hepatitis viruses HAV, HBV, HCV, HDV and HEV.

26. A method according to claim 21 for the treatment and/or prevention of arthritis, pulmonary disorders or lung inflammation, asthma, viral and bacterial infections and bone resorption diseases such as osteoporosis.

27. A method according to claim 21 for the treatment and/or prevention of cachexia, cachexia secondary to infection or malignancy, including cachexia secondary to acquired immunodefiency syndrome (AIDS), AIDS related complex (ARC), pneumonia, herpesvirus and hepatitisvirus.

28. A method according to claim 21 for the treatment and/or prevention of autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus (SLE), discoid lupus erythematosus (DLE), Sjögren´s syndrome, psoriasis, sarcoidosis, and graft-versus-host reactions.

29. A method according to claim 21 for the treatment and/or prevention of endotoxic shock, toxic shock syndrome, reperfusion injury, cardiovascular diseases including atherosclerosis, nephritis, myalgia related to infection, gastrointestinal conditions including inflammatory bowel disease, such as Crohn´s disease and ulcerative colitis.

30. A method according to claim 21 for the treatment and/or prevention of ophthalmic diseases, neoplasia, metastasis, diabetic nephropathy, cardiomyopathy and disorders of the female reproductive system such as endometriosis.

31. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of any one of claims 1-11 optionally in association with diluents, excipients or inert carriers.

32. A pharmaceutical formulation according to claim 31 for use in the treatment of p38 MAP kinase mediated disorders.

33. A pharmaceutical formulation according to any one of claims 31 or 32 for use in the treatment and/or prevention of neurological disorders, multiple sclerosis, viral or bacterial infection and other inflammatory states of the central nervous system, cerebral ischaemia, stroke including cerebral infarction, cerebral haemorrhage and embolization to the vessels of the brain, hepatic diseases, alcoholic liver disease, liver cirrhosis, viral infections of the

liver including infections with hepatitis viruses HAV, HBV, HCV, HDV and HEV, arthritis, pulmonary disorders or lung inflammation, asthma, viral and bacterial infections and bone resorption diseases such as osteoporosis, cachexia, cachexia secondary to infection or malignancy, including cachexia secondary to acquired immunodefiency syndrome (AIDS), AIDS related complex (ARC), pneumonia, herpesvirus and hepatitisvirus, autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus (SLE), discoid lupus erythematosus (DLE), Sjögren´s syndrome, psoriasis, sarcoidosis, and graft-versus-host reactions, endotoxic shock, toxic shock syndrome, reperfusion injury, cardiovascular diseases including atherosclerosis, nephritis, myalgia related to infection, gastrointestinal conditions including inflammatory bowel disease, such as Crohn´s disease and ulcerative colitis, ophthalmic diseases, neoplasia, metastasis, diabetic nephropathy, cardiomyopathy and disorders of the female reproductive system such as endometriosis.

34. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of any one of claims 1-11 in combination with another p38 MAP kinase inhibitor, that acts through a different mechanism, optionally in association with diluents, excipients or inert carriers.

35. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of any one of claims 1-11 in combination with a compound for the treatment of neurological disorders optionally in association with diluents, excipients or inert carriers.

36. A pharmaceutical formulation according to claim 35 wherein the compound for the treatment of neurological disorders is selected from the group tissue plasminogen activators, glutamate receptor antagonists, calcium-channel antagonists, other cation channel blockers, NOS inhibitors, radical scavengers, other kinase inhibitors, chemokine antagonists, purinergic antagonists or protease inhibitors.

37. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of any one of claims 1-11 in combination with an anti-inflammatory compound, optionally in association with diluents, excipients or inert carriers.

38. A pharmaceutical formulation according to claim 37 wherein the anti-inflammatory compound is a steroid, a cyclooxygenase-2 inhibitor, a NSAID, an immunosuppressive agent, a 5-lipoxygenase inhibitor, a LTB_4 antagonist or a LTA_4 hydrolase inhibitor.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02252

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/426, A61P 43/00 // C07D 277/22
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	STN International, File CAPLUS, CAPLUS accession no. 2000:517587, Document no. 133:344452, Simi, Anastasia et al: "Neuroprotective agent clomethiazole attenuates c-fos, c-jun, and AP-1 activation through inhibition of p38 MAP kinase"; & J. Cereb. Blood Flow Metab. (July 2000), 20(7), 1077-1088	1-38
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X	WO 9009174 A1 (AKTIEBOLAGET ASTRA), 23 August 1990 (23.08.90)	1-38
	--	
X	WO 9203134 A1 (AKTIEBOLAGET ASTRA), 5 March 1992 (05.03.92)	1-38
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 February 2001	01 -03- 2001
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02252

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9501968 A1 (ASTRA AKTIEBOLAG), 19 January 1995 (19.01.95), page 3, line 1 - line 35, the claims --	1-38
X	WO 9501967 A1 (ASTRA AKTIEBOLAG), 19 January 1995 (19.01.95), page 4, line 10 - line 33, the claims --	1-38
A	WO 9921859 A1 (GLAXO GROUP LIMITED), 6 May 1999 (06.05.99), page 34, no 16; claims 1, 28, 32 --	1-38
A	WO 9932111 A1 (BAYER CORPORATION), 1 July 1999 (01.07.99), claims 1, 35 (page 121g)), 39, 41; page 102, example 298 -- --------	1-38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02252

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 21-30
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02252

Claims 21-30 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 00/02252

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 00/02252

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